

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY  
CAMDEN VICINAGE**

<b>IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION</b>	<b>MDL No. 2606</b>
<b>THIS DOCUMENT RELATES TO ALL CASES</b>	<b>HON. ROBERT B. KUGLER CIVIL NO. 15-2606 (RBK)(JS)</b>

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**PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS'  
MOTION TO EXCLUDE THE GENERAL CAUSATION  
TESTIMONY OF PLAINTIFFS' EXPERT BENJAMIN LEBWOHL, M.D.**

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### **PRELIMINARY STATEMENT**

Dr. Benjamin Lebwohl is a gastroenterologist and celiac disease specialist at Columbia University. Dr. Lebwohl also has a Master's in biostatistics and teaches epidemiology at Columbia University. He has co-authored multiple articles in the peer reviewed medical literature regarding Olmesartan induced enteropathy ("OIE"), and he has evaluated, diagnosed, and treated multiple OIE patients. Therefore, all of his opinions reflect the current standards of clinical practice and the scientific consensus in the peer reviewed literature, to which he has contributed. Dr. Lebwohl is exactly the type of expert that the Federal Rules and Daubert recognize to be reliable and admissible.

Defendants' Motion is notable for the fact that there is no suggestion that Dr. Lebwohl did not apply an acceptable methodology. In fact, he applied a methodology the defense believes is appropriate, the Bradford Hill criteria. Since the defense cannot argue that Dr. Lebwohl did not apply an acceptable methodology in forming his opinions, the defense instead nitpicks Dr. Lebwohl's analysis within that methodology, and the peer reviewed conclusions resulting therefrom. Of course, Daubert does not address issues that go to the weight of the opinions formed within the acceptable methodology, nor does Daubert address the conclusions reached. Therefore, this motion should be denied.

### **STATEMENT OF FACTS**

Dr. Lebwohl is a board-certified gastroenterologist practicing in the Columbia University Celiac Disease Center. He is a recognized expert in this field, and has published numerous articles in the peer reviewed literature. As stated in his report:

I am a board certified adult gastroenterologist based at the Celiac Disease Center at Columbia University, a major referral center for patients with celiac disease and related disorders. My current academic appointment is Assistant Professor of Medicine and Epidemiology. I joined the faculty of the Center in 2010 after completing a residency in internal medicine at Columbia and a fellowship in digestive and liver diseases, also at Columbia.

....

In addition to my clinical and academic appointments and work, I am on the Editorial Boards of Clinical and Translational Gastroenterology and Digestive Diseases and Sciences, and I serve as a peer reviewer for multiple journals, including but not limited to the New England Journal of Medicine, JAMA, Gastroenterology, and Gut. I have significant research interests, and I have co-authored 88 original research publications in the peer reviewed literature, along with numerous other academic publications.

During my three-year fellowship at Columbia I concurrently obtained a master's degree in Patient Oriented Research from the Department of Biostatistics at the Mailman School of Public Health, also at Columbia.

....

In 2011 I joined the faculty of the Department of Epidemiology at the school. My activities in the Department of Epidemiology have included advising master's students, serving as a research mentor for epidemiological research projects, lecturing to epidemiology students, and participating in the composition and grading of the written examination for PhD candidates in epidemiology. Although my primary area of training is in clinical gastroenterology, I have been invited to adjudicate in the dissertations by epidemiology PhD candidates both within my institution (Columbia) and outside institutions (University of Umea, Sweden and University of Calgary).

(Dr. Lebwohl report at 2-3; Slater Cert., Exhibit 1).

Dr. Lebwohl's methodology involved application of the Bradford Hill criteria:

The evidence to be presented below will consider the Bradford Hill criteria for causality. Strom, et al. These criteria consist of biological plausibility (see above under Medical Literature),[Marietta EV, Nadeau AM, Cartee AK, Singh I, Rishi A, Choung RS, Wu TT, Rubio-Tapia A and Murray JA. Immunopathogenesis of olmesartan-associated enteropathy. Aliment Pharmacol Ther. 2015 Dec;42(11):1303-14.] the strength of the association (see rate ratios reported below by Basson, et al [Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.], the consistency of symptomatology (see adverse event reports and case series below), specificity (the paucity of sprue-like enteropathy reported in other antihypertensives and the quantitative difference when comparing olmesartan use to angiotensin converting enzyme inhibitors),[ Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut. 2016 Oct;65(10):1664-9.] and temporality (see adverse event reports and case series below).

(Dr. Lebwohl's report, at 28-29; Slater Cert., Exhibit 1).

In performing the analysis of the various factors and criteria within the Bradford Hill methodology, Dr. Lebwohl relied upon and analyzed the peer reviewed medical literature in this field, including articles which he co-authored. He also relied upon his own clinical experience in the evaluation, diagnosis and treatment of patients with OIE. (Dr. Lebwohl report at 6-8; Slater Cert., Exhibit 1). Dr. Lebwohl analyzed and applied not only the articles that he has co-authored, but also the other articles in the peer reviewed medical literature that are significant. As stated in his report, there is a firm consensus that Olmesartan causes this condition:

It is now firmly established in the medical literature that a subset of patients utilizing Benicar develop a gastrointestinal syndrome characterized as sprue-like enteropathy, with related gastrointestinal side effects as a result of using this medication. This condition is

referenced internally by Daiichi Sankyo as olmesartan associated enteropathy, and olmesartan induced enteropathy, meaning that the enteropathy is caused by olmesartan. (Allen Feldman, 356:11-15).

(Dr. Lebowhl Report at 5; Slater Cert., Exhibit 1). In this connection, Dr. Lebowhl testified in his deposition to a list of 20 published articles that explicitly or implicitly recognize that Olmesartan causes sprue-like enteropathy in some patients, including his own publications. For example:

- Lagana SM, Braunstein ED, Arguelles-Grande C, Green PH and Lebowhl B. *Spruelike histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers*. J Clin Pathol. 2015 Jan;68(1):29-32. Epub 2014 Oct 23. (Slater Cert., Exhibit 2)
  - **“...the severe syndrome that causes life-threatening diarrhea..”**
- Lebowhl, B., Ludvigsson, J.F. Editorial: *Sprue-like Enteropathy Due to Olmesartan and Other Angiotensin Receptor Blockers – The Plot Thickens*. Aliment Pharmacol Ther 2014; 40:1241-1249. (Slater Cert., Exhibit 3)
  - **“...olmesartan appears to be a prominent, even common, cause of these uncommon conditions.”**
- Mårild K, Lebowhl B, Green PH, Murray JA, Ludvigsson JF. *Blockers of Angiotensin Other Than Olmesartan in Patients With Villous Atrophy: A Nationwide Case-Control Study*. Mayo Clin Proc. 2015 Jun;90(6):730-7. (Slater Cert., Exhibit 4)
  - **“Olmesartan appears to cause a spruelike enteropathy...”**
- Marthey L, Cadiot G, Seksik P and Poudroux P. *Olmesartan-associated enteropathy: results of a national survey*. Aliment Pharmacol Ther. 2014 Nov;40(9):1103-9. Epub 2014 Sep 9. (Slater Cert., Exhibit 5)
  - **“In conclusion, this study shows that olmesartan causes severe and potentially life-threatening enteropathy with or without villous atrophy...”**
- Talley NJ. *Use of olmesartan for  $\geq 1$  year was associated with hospitalization for intestinal malabsorption*. Ann Intern Med. 2015 Dec 15;163(12):JC13. (Slater Cert., Exhibit 6). **“The well**

**conducted database study by Basson and colleagues puts to bed any controversy surrounding the association between the ARB olmesartan and severe intestinal enteropathy pathologically resembling celiac disease. . . . Evidence supporting a causal relation now includes the strength of association, consistent findings, evidence of improvement in most patients after discontinuation, and relapse on drug reintroduction. . . .”**

(Dr. Lebowhl Report at 43-44; Slater Cert., Exhibit 1; Dr. Lebowhl Dep. Tr. 107:15-116:18, 132:15-140:22; Slater Cert., Exhibit 7), (emphasis added).

Dr. Lebowhl also acknowledged that the authors of the Rubio-Tapia study in 2012 were appropriately conservative in first announcing their findings, but pointed out strong language of causation in the article nonetheless:

- Rubio-Tapia A, Herman ML, Ludvigsson JF, Kelly DG, Mangan TF, Wu TT and Murray, JA. *Severe Spruelike Enteropathy Associated With Olmesartan*. Mayo Clin Proc. 2012 Aug;87(8):732-8. Epub 2012 Jun 22.. (Slater Cert., Exhibit 8), (emphasis added).
  - **“Resolution of the presenting symptoms and subsequent histologic improvement after suspension of olmesartan, in the absence of clinical evidence of other diseases associated with enteropathy, suggest that the association is not likely to be due to chance. . . Physicians who encounter patients with diarrheal syndromes should consider medications as a cause.”**

In the course of his report and testimony, Dr. Lebowhl also referenced the peer reviewed website known as “Up To Date,” which is consulted by clinicians across the United States every day in their medical practices. The Up To Date website states in part that the known causes of small intestinal villous atrophy other than celiac disease include Olmesartan. (Lebowhl report at 8-9; Slater Cert., Exhibit 1); (Dr. Lebowhl Dep. Tr. 133:22-134:22; Slater Cert., Exhibit 7).

Dr. Lebowhl also cited to and relied upon the FDA’s finding that Olmesartan can cause spruelike enteropathy in some patients. (Dr. Lebowhl report at 8, 30, 39; Slater Cert., Exhibit 1). The FDA’s public safety announcement of July 3, 2013, as cited by Dr. Lebowhl, disclosed: (1)

the FDA found 23 dechallenges involving Olmesartan, 10 of which involved documented rechallenges; and (2) the FDA found a higher risk as compared to other ARB's for diagnosis of celiac disease. FDA Drug Safety Communication, July 3, 2013 (Slater Cert., Exhibit 9).

Dr. Lebowhl addressed the effort by the defense experts to downgrade the majority of the studies comprising the peer reviewed medical literature on this subject through the misapplication of a hierarchy of evidence analysis. An understanding of the structure and purpose of an RCT, and the inadequacy of such a study to answer the question of general causation here, can be illustrated by a brief discussion of the ROADMAP RCT. In the ROADMAP study, diabetic patients were randomly, and blindly grouped into two groups – those administered Olmesartan and the other given a placebo – in order to detect differences in the time to onset of microalbuminuria, a finding of elevated albumin in the blood which is an early sign of kidney failure. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G; *ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes*. N Engl J Med. 2011 Mar 10;364(10):907-17. (Slater Cert., Exhibit 10). The endgame was to establish an additional indication for physicians to prescribe the drug, which was not even achieved. (Jeffrey Warmke Dep. Tr., 74:14-75:15, 82:2-6; Slater Cert., Exhibit 11).

Dr. Warmke, the Daiichi 30b6 corporate representative, admitted that the ROADMAP study was inadequate to answer the question of whether Olmesartan causes spruelike enteropathy in some patients, because (1) the primary endpoint of the study was to determine whether the time to onset of microalbuminuria was delayed (the case report forms do not even mention gastrointestinal side effects), (2) the population studied, diabetic patients only, was not representative of the population using the medication since non-diabetics also use the drug, and

(3) most important, the study was underpowered to detect differences in the incidence of diarrhea or other representative side effects indicative of OIE – meaning not enough patients were studied (only 2232), and the duration of use was relatively limited in light of the fact that many patients have a time to onset of OIE of more than 3.2 years, which was the median duration of drug use in the study. (Jeffrey Warmke Dep. Tr., 88:8-15, 111:5-11, 272:19-274:11, 362:12-363:23; Slater Cert., Exhibit 11). Dr. Lebwohl explained why it is not scientifically valid to use this Phase 3 study to disprove causation, stating in part, “Indeed the purpose of phase 4 evaluation is to test long-term, less common adverse events induced by the drug; a phase 3 study would not be adequately powered to pick up a signal in the case of a rare event,” and he points to Daiichi’s agreement to the inapplicability of the study on this question:

Daiichi Sankyo employee Jeffrey Warmke testified in his deposition that the ROADMAP study was not designed to study gastrointestinal side effects, and was not adequately powered to study gastrointestinal side effects or any of the secondary endpoints of the study, and the study population was different from the general population taking Benicar in the United States. (Jeffrey Warmke, 88:8-15, 111:5-11, 272:19-274:11, 362:12-363:23). Notwithstanding, Dr. Warmke did acknowledge that there were patients who presented with clinical symptoms of olmesartan enteropathy, including dechallenge and rechallenge, and assessment by Daiichi Sankyo as probably related to the drug.

(Dr. Lebwohl report at 13-14; Slater Cert., Exhibit 1). Dr. Lebwohl testified on this issue in no uncertain terms:

I believe it's deceptive to hold up a randomized trial publication that subsequently evaluates a secondary long-term finding that the initial trial was never designed, nor adequately powered, to detect, for which there were no active surveillance mechanisms to pick up this outcome, and then to use the imprimatur of a randomized trial and the acronym from that randomized trial to somehow prop up the quality of such a study.

(Dr. Lebwohl Dep. Tr., 233:18-234:7; Slater Cert., Exhibit 7). Defense expert Dr. Jerrold Turner, who did no power calculation, agreed that if the ROADMAP study is underpowered it will not

provide reliable information to address this question. (Dr. Turner Dep. Tr., 182:20-184:12; Slater Cert., Exhibit 12). Even the investigators for the study, Daiichi paid consultants Jan Menne, M.D., and Hermann Haller, M.D., who submitted a letter to the editor of the Mayo Clinic Proceedings responding to the Rubio-Tapia publication, acknowledged that the study could be underpowered to identify what they termed a likely rare adverse event. *See* Menne, Haller. *Olmesartan and Intestinal Adverse Effects in the ROADMAP Study*. Mayo Clin Proc. December 2012;87 (12):1230-1232. (“In the ROADMAP study, we could not find a link between the occurrence of diarrhea-associated complications and the intake of 40 mg/d olmesartan. This finding might be because spruelike enteropathy is a rare event.” (Slater Cert., Exhibit 13).<sup>1</sup> Notwithstanding, there were patients in the ROADMAP study who Daiichi confirmed developed the clinical picture of OIE: “Mr. Warmke confirmed that Daiichi Sankyo had first hand knowledge that olmesartan likely caused these symptoms, as this was a study sponsored by Daiichi Sankyo.” (Dr. Lebwohl Report at 13-15, 34-35; Slater Cert., Exhibit 1).

Dr. Lebwohl pointed out in his report that the value of case reports in establishing causation is well-recognized, for example, “Scoring systems, such as the Naranjo Algorithm, a widely used method for grading suspicion of causality, place special emphasis on rechallenge.” (Dr. Lebwohl Report at 27-28; Slater Cert., Exhibit 1). Even more to the point, he cites, “a textbook of Pharmacoeidemiology, Strom B, Kimmel S, Hennessey S. Textbook of Pharmacoeidemiology 2<sup>nd</sup> edition p.23,” as follows:

Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change

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<sup>1</sup> It is important to note that the language in the letter indicating the ROADMAP study did not show an association, was only added to the letter after the letter was clandestinely submitted to and reviewed by Daiichi prior to submission to the Mayo Clinic journal. (Donald Hinman Dep. Tr., 144:12-147:24, 154:7-159:9; Slater Cert., Exhibit 14). The letter does not disclose Daiichi’s review or input into the letter.

returns upon repeat treatment.

(Dr. Lebowhl Report at 27; Slater Cert., Exhibit 1).

Dr. Lebowhl explained further in his deposition why the hierarchy is inapplicable to the evaluation of uncommon adverse drug reactions:

That hierarchy puts systematic reviews and meta-analyses at the very top, usually above what we typically see as the gold standard, the randomized controlled trial; and, indeed, it does put case reports and case series at the bottom. That hierarchy, frankly, is much more useful when looking at efficacy of interventions and is, I would say, hardly relevant when specifically evaluating long-term, uncommon adverse events.

(Dr. Lebowhl Dep. Tr., 148:5-18; Slater Cert., Exhibit 7). Dr. Lebowhl testified that nobody would construct such a study to try to detect a “long-term” uncommon adverse drug reaction. “Randomized controlled trials, you can’t really do that. It’s just not affordable and totally impractical.” (Dr. Lebowhl Dep. Tr., 151:14-22; Slater Cert., Exhibit 7).

On the other hand, Dr. Lebowhl explained in his report why the applicable studies and data, including a mix of epidemiological data, case controlled data, case studies, and case reports, reliably address the question:

In conclusion, there is substantial evidence that, taken on aggregate, establishes the causal relationship between olmesartan and sprue-like enteropathy, to a reasonable degree of medical certainty. The literature began with case series that were followed by numerous case reports worldwide, showing marked improvement of enteropathy upon withdrawal of the drug. This was followed by a population-based cohort study that established a cumulative risk gradient and specificity to olmesartan. The finding of a biologically plausible mechanism provided additional evidence for causality. The significant series of adverse event reports demonstrating patients suffering with the clinical syndrome that characterizes olmesartan enteropathy, and documenting a large number of cases with positive dechallenges and rechallenges, is further important evidence establishing and corroborating the causal relationship.

(Dr. Lebowhl report at 43; Slater Cert., Exhibit 1). In his deposition he explained this further in

the context of “epidemiological research,” rejecting the broad supremacy of the “generic pyramid in terms of quality of research publications,” promoted by the defense. Instead, he explained the complementary interplay and importance of the various categories of studies: “[B]ecause often we can get a convincing narrative regarding the degree of symptomatology and dechallenge and rechallenge data from a case report or case series that we would not be able to glean from a population-based or large cohort study. So it really is about taking all of these into account and acknowledging the limitations of each study type, but not minimizing the strengths either.” (Dr. Lebwohl Dep. Tr., 242:16-243:5; Slater Cert., Exhibit 7).

Dr. Lebwohl also considered and factored in MedWatch reports and adverse event reports available to Daiichi Sankyo, along with the case reports in the literature, recognizing that this evidence forms part of the picture that should be considered in determining whether or not Olmesartan causes sprue-like enteropathy. (Dr. Lebwohl report at 31; Slater Cert., Exhibit 1). Dr. Lebwohl’s report references the adverse event reports documenting numerous compelling rechallenges, as well as compelling adverse event reports within Daiichi’s own files, including some that even Daiichi agrees demonstrate definite or probable causation. (Dr. Lebwohl report at 30-35; Slater Cert., Exhibit 1). Dr. Lebwohl testified: “This is an important piece of the consistency criteria in Bradford Hill that there is a clinical phenotype that’s frequently observed. It doesn’t mean there’s not a spectrum, but that there are some common themes.” (Dr. Lebwohl Dep. Tr., 241:6-16; Slater Cert., Exhibit 7).

Dr. Lebwohl identified the diagnostic criteria for OIE, recognizing and agreeing with the peer reviewed fact that there is a variation in the presenting symptoms and intestinal presentation, both with regard to nature and severity. In his report, Dr. Lebwohl states:

This condition is characterized by delayed onset duration, generally with an onset in the range of months or (more often) years. The

resulting clinical syndrome typically manifests with dehydration and other malabsorptive symptoms such as severe chronic diarrhea and/or vomiting, significant weight loss, abdominal pain, nausea, and related systemic effects. Where intestinal evaluation and biopsies are performed, the specimens generally demonstrate inflammatory changes including partial or total villous atrophy. Findings can include increased intraepithelial lymphocytes and microscopic colitis, among others. There is not a single invariable presentation for this condition, and the condition is ultimately diagnosed based on the clinical presentation and course, with particular attention to positive dechallenge or rechallenge. The findings on pathology can be useful in ruling out potential causes, and for correlation with the clinical presentation and course.

(Dr. Lebwohl report at 6; Slater Cert., Exhibit 1). Dr. Lebwohl testified in his deposition, consistent with his report and the literature, that the presentation of OIE can vary. (Dr. Lebwohl Dep. Tr., 69:20-24, 100:15-101:19; Slater Cert., Exhibit 7)

Moreover, Daiichi's own internal documents recognize the variable presentation of the condition. Dr. Lebwohl discussed the testimony of Daiichi CSPV manager Hideki Tagawa:

Mr. Tagawa discussed an internal powerpoint describing the characteristic symptoms and findings, as well as diagnosis and treatment, for sprue-like enteropathy. The symptoms and findings listed include: severe diarrhea with weight loss, biopsies sometimes reveal intestinal villous atrophy, and inflammation of the lining of the small intestine, and histopathological improvement and improved clinical symptoms when the drug is discontinued. The symptoms listed also include fatty stools, chronic diarrhea, swelling, abdominal bloating, inflammation of skin, tendency to bleed easily, and anemia. The physical exam findings listed include palpebral conjunctiva, oral mucosa, pale skin, pleural fluid, abdominal dropsy, and emaciation (defined as loss of greater than 20% of standard body weight). Finally, the powerpoint indicates that the drug should be discontinued if it is causing the symptoms, an acknowledgment of causation. (Hideki Tagawa, 73-77). Within the same powerpoint is discussion of a fatal sprue-like enteropathy case, where a 70 year old patient had severe diarrhea, dehydration, and a 30 kg weight loss. The conclusion by Daiichi Sankyo is that **"causality cannot be denied based on available information," and confirms the drug was the cause of death.** (Hideki Tagawa, 57-60). Mr. Tagawa also confirmed that another Japanese language document indicated that the Japanese label was modified to

**include information about sprue-like enteropathy, because “for the symptoms of severe diarrhea, a causal relationship with drugs containing olmesartan could not be denied.” (Hideki Tagawa, 69-70).**

(Dr. Lebowhl Report at 41; Slater Cert., Exhibit 1), (emphasis added).

The defense cites to the Rubio Tapia article, specifically Table 3 setting forth clinical features of the condition, in an effort to establish that Dr. Lebowhl’s diagnostic criteria is too broad. (Defense Brief at 5-6). In fact, the defense actually helps to prove the Plaintiffs’ point. First, Defendants are highlighting and acknowledging that the seminal article in this area lists objective features that support the diagnosis of OIE. Dr. Lebowhl certainly does not dispute that these objective features are consistent with and diagnostic of OIE. However, Dr. Lebowhl is now testifying approximately 5 years following the publication of that initial article, with the benefit of years more of clinical experience, as well as many articles and case reports published in the peer reviewed literature further refining the contours of the syndrome. Dr. Lebowhl pointed out that “the subsequent authors had the further benefit of further data and time.” (Dr. Lebowhl Dep. Tr., 112:18-113:5; Slater Cert., Exhibit 7). In fact, this literature highlights and emphasizes the importance of documented dechallenges and rechallenges in the diagnostic process, inasmuch as the unifying factor as between most if not all of these reports is that the patient improved/resolved his or her symptoms upon withdrawal of the medication (dechallenge), and in some cases the symptoms then returned upon reintroduction of the medication (rechallenge). These dechallenges and rechallenges are very important evidence of causation relied on by Dr. Lebowhl. (Dr. Lebowhl Dep. Tr., 372:17-373:21; Slater Cert., Exhibit 7).

The Defendants also criticize Dr. Lebowhl’s analysis of what the defense terms the 4 epidemiologic studies in this area, aside from the Basson study (see below) which the defense attempts to ignore at every turn. First, as established above, the ROADMAP study was neither

designed or powered to address the question of whether Olmesartan causes sprue-like enteropathy in some patients. Defendants suggest that Dr. Lebwohl is somehow inconsistent in his rejection of the ROADMAP study as an epidemiologic source to evaluate the question of general causation, while relying upon individual adverse event reports for patients in the Olmesartan arm of this randomized control trial, to show that some patients did develop OIE. There is absolutely nothing inconsistent in this analysis. Due to the infrequent nature of this condition, the number of patients studied in the ROADMAP study was too few to provide valid data on the overall question of general causation. However, the identification of specific patients who developed OIE, confirmed by internal causality assessments rendered by Daiichi physicians applying differential diagnosis and medical judgment, is compelling.

Second, the Greywoode study was co-authored by Dr. Lebwohl, Dr. Lagana, and others. (Slater Cert., Exhibit 15). Dr. Lebwohl explained the design of the study and the conclusions to be drawn, testifying:

It turns out that the great majority, about 99 percent of them, weren't taking olmesartan and so one thing that we didn't know at the outset of that study -- and this is the way research works, is one comes up with a study design and a hypothesis, but before you actually get a look at the data, we didn't really know how popular olmesartan was or unpopular it was -- so we found, unfortunately, that this exposure wasn't very common in either group, which really limited our ability to draw firm conclusions.

\* \* \*

We did not find that olmesartan was statistically associated with chronic diarrhea. In that analysis of only about 102 or 103 patients who I take olmesartan, I believe I touched on this earlier, but just to clarify, this was a case-control study that we designed during the early phases of our understanding of olmesartan enteropathy and we wanted to know to what degree the current, or at the time, description of that clinical phenotype represented the tip of an iceberg.

(Dr. Lebowhl Dep. 145:12-146:1, 238:21-239:9; Slater Cert., Exhibit 7). The fact that this study was underpowered to answer a question of general causation is not just Dr. Lebowhl's opinion. The Greywoode article itself recognized that it was underpowered: "There was also a relatively small prevalence of use of olmesartan (0.7%-1%) among study patients, limiting the power of this analysis." See Greywoode, et al., *supra*. Other peer-reviewed publications reached the same conclusion: "The [Greywoode] study was limited, however, by the small number of patients taking olmesartan: 22 patients (1%) in the esophagogastroduodenoscopy group and 83 patients (0.7%) in the colonoscopy group." Choi EY, McKenna B. *Olmesartan-Associated Enteropathy, A Review of Clinical and Histologic Findings*. Arch Pathol Lab Med. 2015 Oct;139(10):1242-7 (Slater Cert., Exhibit 16).

Third, Lagana et al., was a study of a handful of patients who presented for endoscopies at Columbia with a complaint of abdominal pain. (Slater Cert., Exhibit 2). "The Lagana paper was interested in abdominal pain, and chronic diarrhea was not the subject of that paper." (Dr. Lebowhl Dep. 238:6-9; Slater Cert., Exhibit 7). Very few of those patients were actually taking Olmesartan and as the study itself indicates, it was underpowered to answer the question. "A larger sample size may have been useful, as it is possible that olmesartan causes a true increase in duodenal histopathological abnormalities but that our study was underpowered to detect this effect." Lagana, et al., *supra*. (Slater Cert., Exhibit 2). Similarly, Dr. Lebowhl stated in his report that, "the study was likely underpowered to detect a signal of subtle histologic abnormalities related to olmesartan" and that Lagana et al., and Greywoode et al., "should be seen in the context of studying and defining the boundaries of the condition." (Dr. Lebowhl Report at 16-17; Slater Cert., Exhibit 1).

Finally, with regard to Padwal (Slater Cert., Exhibit 17), Dr. Lebowhl was generally aware of the study but did not address it in his report, however he added it to his reliance list after

reviewing the defense expert reports and was fully prepared to discuss it at his deposition. (Dr. Lebwohl Dep. Tr., 94:8-15; Slater Cert., Exhibit 7). However the defense chose to ask no substantive questions about this study at his deposition.

Defendants also take issue with Dr. Lebwohl's opinions regarding the question of whether there is a dose relationship to this condition. Dr. Lebwohl testified that the recommended dosage of Olmesartan is sufficient to cause this condition, and Dr. Lebwohl explained that it is the cumulative dose effect that leads to the condition. (Dr. Lebwohl Dep. Tr., 221:20-222:16; Slater Cert., Exhibit 7). Dr. Lebwohl analogized OIE to celiac, explaining that there are patients who eat gluten without incident for long stretches of their lives before they develop celiac disease. (Dr. Lebwohl Dep. Tr., 67:20-68:11; Slater Cert., Exhibit 7). This concept of cumulative dose response over the course of time is strongly supported in literature, for example the Basson study. In Basson, the relative risk increased 10-fold after patients utilized Olmesartan for more than 2 years. Basson M, Mezzarobba M, Weill A, Ricordeau P, Allemand H, Alla F and Carbonnel F. *Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study*. Gut. 2016 Oct;65(10):1664-9. Epub 2015 Aug 6.. (Slater Cert., Exhibit 18). The same also holds true for the Rubio Tapia article which talked about the median duration of use before onset of symptoms in excess of 3 years. (Slater Cert., Exhibit 8).

Finally, Dr. Lebwohl discussed the plausible biological mechanism for OIE in his report (Dr. Lebwohl Report at 20-21), and in his deposition, "The Marietta paper is also relevant [to biological plausibility], but I believe that the link between these symptoms and this clinical phenotype and olmesartan can be explained by certain histological findings that have been identified, just like the link between gluten and feeling ill has biological plausibility, namely villous atrophy and other histologic findings, among others." (Dr. Lebwohl Dep. Tr., 255:4-13;

Slater Cert., Exhibit 7). Notably, Defendants' expert Dr. Jerrold Turner agreed one need not establish a mechanism at the molecular level and that this proposed mechanism is a plausible biological mechanism. (Dr. Turner Dep. Tr., 232:22-233:2, 233:13-234:2; Slater Cert., Exhibit 12).

In this context, it is important to note that Dr. Lebowhl is a specialist with regard to celiac disease. Dr. Lebowhl considers and analogizes to celiac disease, because the clinical and pathologic presentations are so similar between the two conditions. This is a peer reviewed fact. "[I]t is likely that prior to the first report of this clinical entity in June 2012, patients with this condition would be misdiagnosed with celiac disease." Marild, et al. at 7; Slater Cert., Exhibit 4). Indeed, the evaluation of the condition via analogy is one of the nine Bradford Hill criteria.

## **LEGAL ARGUMENT**

### **I.**

#### **DR. LEBWOHL'S METHODOLOGY IS RELIABLE**

The admissibility of expert testimony is determined pursuant to Rule 702, which incorporates the Daubert standard.

In determining reliability, a court may look to several non-exhaustive factors, including:

(1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Geiss v. Target Corp., 2013 WL 4675377 at \*4 (D.N.J. Aug. 30, 2013) (Slater Cert., Exhibit 19) (quoting Elcock v. Kmart Corp., 233 F.3d 734, 745-47 (3d Cir. 2000). "Rule 702 has a liberal

policy of admissibility.” Geiss, 2013 WL 4675377 at \*4 (citing Pineda v. Ford Motor Co., 520 F.3d 237, 243 (3d Cir. 2008), other citations omitted. The Third Circuit, “made clear in Paoli II, an expert’s level of expertise may affect the reliability of the expert’s opinion.” Elcock, 233 F.3d 734, 746 (quoting In re Paoli R.R. Yard PCB Litigation, 35 F.3d 717, 741 (3d Cir. 1994) (“Paoli II”). Dr. Lebwahl’s extensive qualifications, including publication of peer reviewed literature on this subject, should therefore bear upon the reliability inquiry. See Elcock, 233 F.3d at 746; Paoli II, 35 F.3d at 741.

Very recently, in the Xarelto litigation, a series of similar Daubert motions were summarily denied, with the court succinctly opining that the plaintiffs’ experts applied the proper methodology, and relied on peer reviewed literature, thus the balance of the defense’s criticisms went to the weight of the opinions, not admissibility. See In re Xarelto (Rivaroxaban) Prod. Liab. Litig., Case No. 2:14-MD-02592, Doc 6198, 2017 WL 1352860 (E.D.La, April 13, 2017). (Slater Cert., Exhibit 20). With particular relevance to this case, the Court noted that plaintiffs’ gastroenterologist, Dr. Winstead, “attests that he used the same methods he uses to evaluate and treat his patients” in writing his expert report. Id., 2017 WL 1352860 at \*5. “The Court finds Dr. Winstead is qualified by virtue of his training and experience. He reaches his conclusion that NOACs, and specifically Xarelto, can cause bleeding without underlying pathology through his experience, the presence of the drug in Plaintiff’s stool, peer reviewed literature, and Xarelto’s label. Defendants may cross-examine Dr. Winstead on these issues at trial.” Id. The same result is appropriate here.

Dr. Lebwahl applied the methods and knowledge he uses in his clinical and academic work at Columbia University, and offers an opinion that he has expressed in peer reviewed medical literature. Nevertheless, Defendants try to flip the standard on its head and incredibly criticize Dr.

Lebwohl for concluding, entirely independent of and preceding litigation, that Olmesartan can cause enteropathy. They argue that Dr. Lebwohl should be excluded because he “approached the scientific record with the preconceived conclusion that olmesartan can cause sprue-like enteropathy.” (Defendants’ brief at 8). In fact, the law is clearly to the contrary. “Expert opinions generated as the result of litigation have **less credibility than opinions generated as the result of academic research or other forms of ‘pure’ research.**” Soldo v. Sandoz Pharmaceuticals Corp., 244 F.Supp.2d 434, 527 (W.D.Pa. 2003), emphasis added. It is well established that experts who form their opinions solely for purposes of litigation (**Defendants’ experts here**) should be scrutinized more closely than experts who formed their opinions based upon the results of their independent, peer reviewed research.<sup>2</sup>

Dr. Lebwohl has conducted research on OIE, he has published his conclusions about OIE in the peer-reviewed literature, he treats his patients based upon the conclusions he has reached about OIE, and other physicians rely on his diagnoses and recommendations regarding OIE.

As a result of my knowledge of this condition, I adopted a practice where, when a referring colleague calls me, asking me to see a sick and complicated outpatient on short notice as a second opinion, I will first ask them if the patient is taking olmesartan, which has occasionally led to a rapid diagnosis and resolution of the problem while under the care of the referring physician, without the patient even coming to our center for formal evaluation.

<sup>2</sup> See Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1317 (9th Cir.1995) (“Daubert II”) (“One very significant fact to be considered is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying.”); Johnson v. Manitowoc Boom Trucks, Inc., 484 F.3d 426, 434 (6th Cir. 2007) (“This Court has recognized for some time that expert testimony prepared solely for purposes of litigation, as opposed to testimony flowing naturally from an expert’s line of scientific research or technical work, should be viewed with some caution.”); Wehling v. Sandoz Pharmaceuticals Corp., 162 F.3d 1158 (Table), 1998 WL 546097, \*3 (4th Cir. 1998) (“Another significant fact weighing against admitting the testimony is where, as here, the expert developed his opinions expressly for the purposes of testifying.”); In re Asbestos Products Liab. Litigation, 2011 WL 605801, \*7 (E.D.Pa. 2011) (“We acknowledge that the development of a particular opinion for the express purpose of litigation may be considered as a factor weighing in favor of preclusion.”); Bd. of Trustees of AFTRA Retirement Fund v. JPMorgan Chase Bank, N.A., 2011 WL 6288415, \*7 (S.D.N.Y. 2011) (“[C]ourts are especially skeptical of methodologies created solely for purposes of litigation.”).

(Dr. Lebowhl report at 8; Slater Cert., Exhibit 1).

**A. Dr. Lebowhl Reliably Applied the Bradford Hill Criteria, and Defendants' Criticisms Go To Weight, Not Admissibility.**

In reaching his conclusions, Dr. Lebowhl applied the Bradford Hill criteria, which are “nine factors widely used in the scientific community to assess general causation.” Glynn v. Merck Sharp & Dohme Corp., 2013 WL 1558690, \*3 (Apr. 10, 2013) (quoting Gannon v. U.S., 292 Fed. Appx. 170, 173 (3d Cir. 2008) (Slater Cert., Exhibit 21). “One or more of the factors may be absent even where a causal relationship exists and...no factor is a sine qua non of causation.” Glynn, 2013 WL 1558690, at \*3, citing Magistrini v. One Hour Martinizing Dry Cleaner, 180 F.Supp. 2d 584, 593 n. 9 (D.N.J. 2002). Dr. Lebowhl weighed the Bradford Hill criteria and reached the conclusion, which has been subjected to peer-review, that Olmesartan causes spruelike enteropathy. This suffices as an acceptable methodology and should end the inquiry.

Defendants level no serious attacks on Dr. Lebowhl's methodology, rather they focus on his analysis within that methodology, which goes only to the weight of the testimony, not admissibility. For example, they argue that he should have robotically weighed the epidemiological studies based upon their position in the generic hierarchy of evidence. Dr. Lebowhl clearly explained why he rejects that approach, and Defendants are free to address this on cross-examination. Indeed, Dr. Lebowhl testified:

That, though, is a generic hierarchy that I'd say is not particularly applicable to the issue at hand, which is, does this agent cause in the long term an adverse event. Randomized trials don't last long enough to pick up adverse events and so to cite the hierarchy of evidence or to diminish the importance of case reports and case series is, I think, a diversion.

(Dr. Lebowhl Dep. Tr., 149:9-19; Slater Cert., Exhibit 7). Dr. Lebowhl's opinion that the defense's reliance on RCT's is misplaced here is fully consistent with the law. “The experts in this case recognize that the types of studies the defendants claim are needed to make an opinion reliable—

human prospective placebo-controlled clinical trials—are not feasible or ethical.” In re Tylenol (Acetaminophen) Marketing, Sales Practices, & Products Liab. Litigation, 198 F.Supp.3d 446, 457 (E.D.Pa.2016).

Defendants accuse Dr. Lebwohl of “picking and choosing” the evidence upon which he relies. Even if true, which it is not, this goes to the weight of the evidence, and the case cited by Defendants provides no support for their argument. In Lust, plaintiff’s expert asserted an opinion that the drug, Clomid, was capable of causing *any kind* of birth defect since it was thought to cause some types of birth defects. Lust By & Through Lust v. Merrell Dow Pharmaceuticals, Inc., 89 F.3d 594, 596 (9th Cir.1996). The Ninth Circuit quoted the District Court as saying:

The problem in this case is that Dr. Done . . . has merely interpreted the work of others, **without informing the Court what those works are or what conclusion the original authors reached**. Dr. Done has seen fit to “pick and chose” [sic] from the scientific landscape and present the Court with what he believes the final picture looks like. This is hardly scientific.

Lust, 89 F.3d at 596. That is clearly not the situation in this case.

Instead, Dr. Lebwohl has thoroughly explained the relative significance of each category of evidence, for example why he gives more weight to the Basson study, less weight to the other studies, and why the dechallenge and rechallenge evidence are so important in this case. See In re Zoloft (Sertraline Hydrochloride) Products Liab. Litigation, 26 F.Supp.3d 449, 461 (E.D.Pa.2014) (“[T]he accepted scientific practice is for an expert to explain why she gives more weight to certain studies in forming her opinion, discussing methodology, power, and other key factors; In re Avandia Marketing, Sales Practices & Products Liab. Litigation, 2011 WL 13576, \*9 (E.D.Pa, Jan. 4, 2011) (“When he rejects research that does not support his opinion, he explains why he finds that research flawed and not compelling. That is, his approach to the data was scientifically reliable. Any inconsistency in Dr. Brinton’s opinions over time, and any flaws in his conclusions,

go to weight, not admissibility.”) (Slater Cert., Exhibit 22).

In Glynn, the motion to preclude plaintiffs’ expert on general causation under Daubert was denied because, as here, the expert considered the Bradford Hill factors, and the criticisms went to the weight, not admissibility of the testimony. The Court concluded, “Defendant is free to address these issues on cross-examination...” Glynn, 2013 WL 1558690, at \*4.

**B. Dr. Lebwohl’s Conclusion Can Be – and *Has Been* – Tested.**

The question of whether Olmesartan causes enteropathy can be and has been tested with dechallenge and rechallenge tests.

A test is a “dechallenge” test when a drug that is suspected of causing a certain reaction is withheld to see if the reaction dissipates. The drug may then be reintroduced in a “rechallenge” to see if the reaction reoccurs. **These reports, which may be analogized to controlled studies with one subject, can be particularly useful in determining whether a causal relationship exists.**

Rider v. Sandoz Pharmaceuticals Corp., 295 F.3d 1194, 1199 (11th Cir.2002), emphasis added.

Dr. Lebwohl has actually published a study documenting positive dechallenges with improvement in clinical symptoms and biopsy results following cessation of Olmesartan in 16 patients, and, “Notably, one patient who had symptomatic improvement off olmesartan was then rechallenged with the medication and symptoms recurred.” DeGaetani M, Tennyson CA, Lebwohl B, Lewis SK, Abu Daya H, Arguelles-Grande C, Bhagat G and Greene PH. *Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma*. Am J Gastroenterol. 2013 May;108(5):637-53, at 650 (Slater Cert., Exhibit 23). The article includes Olmesartan in the class of medications that, “have been considered to cause villous atrophy.” Id.

Ordinarily, a key question to be answered in determining whether a theory or technique is scientific knowledge that will assist the trier of fact will be whether it can be (and has been) tested. Scientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry.

Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 593, 113 S.Ct. 2786, 2796, 125 L.Ed.2d 469 (1993) (quoting Green, Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of *Agent Orange* and Bendectin Litigation, 86 Nw.U.L.Rev. 643 (1992)).

Likewise, the Reference Manual on Scientific Evidence stresses the strength of dechallenge evidence.

If an agent is a cause of a disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease. This has been the case, for example, with cigarette smoking and lung cancer. In many situations, however, relevant data are simply not available regarding the possible effects of ending the exposure. But **when such data are available and eliminating exposure reduces the incidence of disease, this factor strongly supports a causal relationship.**

Federal Judicial Center, Reference Manual on Scientific Evidence, Reference Guide on Epidemiology, at 605 (3d ed. 2011). In accord with these authorities, Dr. Lebwohl testified that some of the strongest evidence of causation in this case is the dechallenge and rechallenge data: “[I]t’s the case reports with multiple dechallenge and rechallenge in multiple contexts from around the world that are actually most helpful” in understanding olmesartan enteropathy. (Dr. Lebwohl Dep. Tr., 373:7-12; Slater Cert., Exhibit 7).

The balance of the Defendants’ arguments, primarily based on mischaracterizations of case law and Dr. Lebwohl’s deposition testimony, go only to the conclusions reached, and the weight to be given those conclusions. For example, Defendants cite Pick v. Am. Med. Systems, Inc., 958 F.Supp. 1151 (E.D.La.1997), claiming that the expert opinion in Pick was declared unreliable where “the clinical symptoms [the expert] associates with SCD are so varied and general they cannot be corralled into a specific diagnostic criteria.” (Defense brief at 8; quoting Pick, at 1178). However, the expert there was an isolated outlier:

Assuming without deciding that Systemic Coccal Disease even exists, Dr. Hyman's methodology to detect it fails the *Daubert* test. By his own, and at times proud, admission his methodology is unique to him and Dr. Deming and runs counter to the established procedures of virtually all other laboratories and medical facilities, all of which he simply dismisses as being mistaken.

Id. at 1177–79. Pick has no application to Dr. Lebowhl's opinions, although it has direct application to the defense experts.

Defendants also cite Kilpatrick v. Breg, Inc., 2009 WL 2058384, \*4 (June 25, 2009), aff'd, 613 F.3d 1329 (11th Cir. 2010), arguing that Dr. Lebowhl's testimony should be excluded because the "medical literature supporting his claim is still a 'developing science.'" In Kilpatrick, the causation question was highly complex and specific:

If anything, determining causation in this case requires an even more complex logical chain than the typical toxic tort case, because the key issue is not merely whether a chemical compound could and did cause injury, but whether that compound as delivered via a particular medical device inserted in a particular location (within Kilpatrick's shoulder joint) could and did cause injury.

Kilpatrick, 2009 WL 2058384\*4. In this narrow circumstance, the court found that the expert made too great a leap in extrapolating from studies that did not address the question.

This Court has reviewed the studies Poehling claims to rely upon, and found that Poehling's extrapolations from them regarding causation are not warranted. What is more, Poehling, when pressed, essentially admits the same thing.

Id. at \*9. That case hardly speaks to the situation here.

**CONCLUSION**

For the foregoing reasons, Defendants' motion to preclude Dr. Lebowhl's opinions under Daubert should be denied. Dr. Lebowhl applied a valid methodology, relying primarily on peer reviewed literature that he has contributed to. Whatever criticisms the defense may have are directed to Dr. Lebowhl's conclusions, which are fully consistent with the consensus in the peer reviewed literature, and can be explored on cross-examination at trial.

Respectfully,

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